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Rita Pissarra Teixeira

Cardiac Biomarkers in Neonatology:

BNP/NTproBNP, Troponin I/T, CKMB and Myoglobin, a systematic Review

Biomarcadores Cardíacos em Neonatologia:

BNP/NTproBNP, Troponina I/T, CKMB e Mioglobina, uma revisão sistemática

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Cardiac Biomarkers in Neonatology: BNP/NTproBNP, Troponin I/T, CKMB and Myoglobin, a systematic review

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R. Baden-Powell

Aos príncipes e princesas do Kastelo

(centro de cuidados continuados e paliativos pediátrico)

Cardiac Biomarkers in Neonatology: BNP/NTproBNP, Troponin I/T, CKMB and Myoglobin, a systematic review

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Abstract

Cardiac biomarkers play a central role in myocardial injury and heart failure in adult patients however their clinical relevance in diagnosis and management in neonatology is not clearly stablished. The aim of this systematic review was to evaluate the recent literature on BNP/NTproBNP, Troponin I/T, CKMB and Myoglobin and their relationship with different pathologies of the newborn.

A total of 67 articles were included to undergo data extraction, after a first text and abstract analysis and a second full-text analysis, using the PubMed database.

Evidence show that cardiac biomarkers are a useful and fast diagnostic tool with great potential for becoming as important as clinical and echocardiographic findings in pathologies of the heart. BNP/NTproBNP and Troponin I/T demonstrated to be the ones with greater value. BNP/NTproBNP is of particular significance in the diagnosis and management of patent ductus arteriosus, as it has a good correlation with diagnosis, treatment and prognosis. Troponin T may be a beneficial additional marker for this disease, correlating with ductal significance and treatment response. Moreover, BNP/NTproBNP can be used, with other clinical and laboratory findings, in the diagnosis and as a guide for treatment in pulmonary hypertension and in the diagnosis and management of cardiac sequela in bronchopulmonary dysplasia. Troponin I/T finds its clinical importance in perinatal asphyxia as a marker of myocardial injury and a reliable indicator of severity and mortality.

Further studies with larger cohort populations are needed for stablishing the cutoff values specific for each neonatal pathology allowing its early and proper management.

Keywords

Cardiac biomarkers; BNP; Troponin; CKMB; Myoglobin; neonatal intensive care

Introduction

Cardiac biomarkers reflect the structure and function of the heart, being widely used in the management of myocardial injury and heart failure in adult patients [1,2]. Their use in pediatrics, especially in neonatology, has been increasing but their clinical role as a guide for diagnosis, treatment and prognosis in neonatal diseases, is not clearly stablished and no current guidelines exist to guide their routine use [3,4].

B-type natriuretic peptide (BNP) and its inactive by-product N-terminal-pro-BNP (NTproBNP) are markers of volume expansion and pressure overload of the heart. BNP release results in improved myocardial relaxation and it antagonizes the response to the activated renin-angiotensin-aldosterone system [5]. The plasmatic half-life of BNP is 20 min whereas for NTproBNP is 60 min [6]. BNP and NTproBNP can be simply measured with commercial kits including bedside tests, with good correlation between both biomarkers [7].

Troponin (Tn) I and T, Creatine Kinase-MB (CKMB) and myoglobin are markers of cardiac injury [2]. The troponin complex, part of the sarcomere, regulates the cardiac and skeletal muscle contraction. It consists of three subunits: TnC (binds calcium ions and regulates the activation of actin filaments), TnI (inhibits muscle contraction in the absence of calcium) and TnT (binds troponin to tropomyosin and actin) [8]. TnC is not used as a marker of cardiac injury as it exists in highly homogenous isoforms whereas TnI exists only in three isoforms (one specific to the myocardium) and TnT has four isoforms specific to the cardiac muscle [9]. After a cardiac injury, troponins become detectable in the blood around the 2^{nd} to the 4^{th} hour, with a peak at 12 hours and remain high for 7 to 10 days [10].

CKMB is one of the three creatine-kinase isoenzymes expressed in the heart (≈22% of the total CK content) and skeletal muscle (≈1-3%). It is usually undetectable or in low levels in the blood except in the presence of both heart and skeletal diseases [11]. CKMB release in the blood after an injury is close of that of troponins, but its levels remain elevated for shorter time [12].

Myoglobin is a cytoplasmic protein in striated cardiac and skeletal muscle with oxygen-carrying and reservoir function and a rapidly release after myocardial damage [11].

Tn I and T show higher sensitivity and negative predictive value than CKMB in detecting myocardial injury [13] with CKMB and in particular myoglobin not offering additional diagnostic value in diagnosing for example acute myocardial infarction in adult patients [14].

The aim of this systematic review was to evaluate the recent literature on Cardiac Biomarkers (BNP/NTproBNP, TnI/T, CKMB and myoglobin) and their relationship with different pathologies and diagnosis in Neonatology.

Methods

Protocol

A review was conducted based on the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Eligibility Criteria

Clinical trials, prospective and retrospective observational studies aiming the use of cardiac biomarkers in neonatology were considered. Measurements of the biomarkers BNP/NTproBNP, TnI/T, CKMB and Myoglobin in the cord blood, arterial and venous blood were included. Neonates with or without pathology were considered. Pathologies diagnosed prior to birth or conditions affecting the neonate in intrauterine life were not the purpose of this review.

Studies with these biomarkers levels in neonates without disease versus with disease were addressed, as the use of these biomarkers versus actual diagnostic methods or its inexistence in neonatal age, in newborns with pathology.

Records from January 1990 to June 2016 were considered. The search strategy was restricted to studies concerning human subjects that were available in the English language. Data concerning simultaneously neonates and children/adult patients were included, unless the neonates group were not separated from the rest of the groups studied.

Duplicate articles, comments, case series, narrative or systematic reviews and meta-analyses, as well those not related with the purpose of the study were excluded.

Information sources

On June 1, 2016, a PubMed literature search focused on cardiac biomarkers in neonatology was executed. The following MESH terms and text key words were used: “natriuretic peptide, brain” or “pro-brain natriuretic peptide” or “troponin i” or “troponin t” or “myoglobin” or “creatine kinase, mb form” and “infant, newborn” or “neonatology”.

Study Selection

First analysis included a screening of all article titles and abstracts to identify relevant studies. References were crosschecked in all selected articles, to identify articles missed by the initial search strategy, using the same inclusion and exclusion criteria.

Eligibility was assessed by 2 authors (R.P.T. and A.L.N.) in all potentially relevant articles. Disagreements were resolved by discussion.

Data items

Data were extracted on type of pathology, cord/plasma biomarkers levels and age. When reported in the study, type and biomarkers concentrations of controls and correlation to echocardiographic measurements were collected.

Summary measurements and synthesis of results

The principal summary measures included mean cord/plasma biomarkers levels, grade of correlation and risk ratio. Data from different studies were registered, then combined, and summarized according the type of biomarker.

Results

Study selection

A detailed flowchart of the systematic review is presented in **Figure 1**. Through PubMed searching 373 articles were identified. After duplicates removed, 372 articles were included in the first analysis: screening of the reference list based on their titles and abstracts. This step was crosschecked between the two researchers. After the first step, 273 articles were excluded based on the title and abstract: 27 articles did not include a group of only neonates; 22 articles did not focus on pathologies diagnosed after birth; 2 articles were animal studies; 34 articles were comments, reviews or case series and 188 articles did not address our outcomes of interest. A total of 5 articles were not assessed, since we did not have access to full text. Therefore, 94 full-text retrieved articles were carefully assessed. From these, 27 were excluded based on our previously defined exclusion criteria: 7 articles did not include a group of only neonates and 20 articles did not address our outcomes of interest. In the end, 67 articles were included to undergo data extraction.

Study characteristics

Study characteristics are summarized in the **Table 1**. Prospective and retrospective case-controls studies and cohort studies were included. Most of the studies were single-center and with an observation period from at least one year, including studies from different countries such as USA, Italy, UK, Ireland, Korea, Thailand, Portugal, India and others.

Results of individual studies

BNP and NTproBNP

BNP/NTproBNP in Patent Ductus Arteriosus

Several studies concerning BNP and NTproBNP in neonatology focused on their potential role in patent ductus arteriosus (PDA). BNP concentrations were significantly higher in preterm neonates with echocardiographically proven PDA ($p<0.001$) [15,16] and no difference was observed between term and preterm without PDA [16]. Higher levels of BNP correlated with increasing magnitude of the PDA [17,18].

In fact, in infants with an hemodynamically significant patent ductus arteriosus (hsPDA) (defined by a left atrial/aortic root (LA/Ao) ratio >1.5 and a ductal diameter >1.4mm on echocardiography [15]), mean BNP levels were significantly higher than those with either no hsPDA [19,20] or non PDA ($p<0.005$) [19,21]. Moreover, a study concerning hemodynamically significant left-to-right (hsLtR) shunts as a group, found that BNP concentrations were significantly more elevated in neonates with hsLtR shunts compared to cyanotic heart disease or no heart disease ($p<0.0001$). However infants with hsPDA had significantly higher levels of BNP compared to the rest of hsLtR shunts ($p=0.016$) [22].

Mean BNP correlated positively with echocardiographic magnitude of the ductal shunt: ductal diameter, LA/Ao ratio and diastolic flow velocity of the left pulmonary artery [15,18,20,21]. The LA/Ao ratio was the mostly related parameter to BNP concentration in the newborns [16].

BNP concentrations were positively correlated with the need of ductus intervention and not only to the presence of PDA. In addition to ductal diameter >1.5 mm, BNP had the best predictive value (PPV): 91% for the need of treatment [23]. Also significant differences in levels of BNP were demonstrated with increasing ventilatory support [17]. A study showed that a BNP level more than 250 pg/mL at day 2 indicated the need of medical treatment (OR=5.0) and that above 2000 pg/mL within the first 5 days indicated the need of surgical correction (OR=52.2) [24]. Moreover, successful closure was reflected by a corresponding decrease in BNP [15,19] and BNP concentrations on days 3, 5 and 7 remained higher in infants with persisting PDA [15].

Regarding NTproBNP, studies showed main results similar to BNP results. In newborns with a PDA, NTproBNP levels were significantly higher compared to those with spontaneous PDA closure, ($p<0.001$) [25] and they could identify neonates with a high risk of developing an hsPDA from day 1 to 7 [26-29]. Moreover, low levels of NTproBNP could detect neonates with a closed ductus [26] and higher levels could identify those with later treated or persistent PDA [30]. Additionally, NTproBNP levels were significantly elevated in a PDA that could later develop severe intraventricular hemorrhage or death compared to a PDA without complications [25].

NTproBNP correlated with echocardiographic flow patterns as those above mentioned for BNP [26,29-31] and successful ductus closure was also correspondent with a decline in NTproBNP levels [27,32]. In fact, a study using a predetermined cutoff level of NTproBNP [32] showed that using its levels on day 2 to guide early treatment with indomethacin reduced later onset of hsPDA, neither reopening of ductus or PDA ligation and reduced the exposition to indomethacin, only 11% [33]. Accordingly, NTproBNP on day 3 could predict whether a neonatal physician blinded to results would treat a PDA [27].

A study comparing both biomarkers stated that BNP and NTproBNP seem to be similarly useful in the diagnosis of PDA and evaluation of its magnitude in preterm neonates. Correlation with PDA size for BNP was $r=0.35$ ($p=0.0066$) and for NTproBNP was $r=0.31$ ($p=0.018$) [34].

The cutoffs levels proposed from different studies to diagnose an hsPDA of both BNP and NTproBNP are described in **Table 2**, with respective area under the curve, sensitivity, specificity, positive and negative predictive value.

BNP/NTproBNP in Congenital Heart Defect

A study revealed that BNP values were significantly higher ($p<0.001$) in the whole group of congenital heart defect (CHD) patients than in controls but considering the different CHD groups separately, all groups, except for of right ventricular pressure/volume overload, showed significantly higher values compared to control group ($P\leq0.0001$). The authors attribute the difference in the groups to the low number of patients in the right ventricular pressure/volume overload group [35].

In a different study with neonates undergoing surgery for CHD, the preoperative BNP levels were higher in infants with CHD, compared with age-matched controls ($p<0.001$), with a good diagnostic accuracy. A cutoff value of 363.5 pg/mL had a sensitivity of 87.4%, a specificity of 87.6% for diagnosing CHD. BNP values were higher than older children values, and differently from them, they decreased immediately after surgery [36].

In critical CHD infants with ductal-dependent systemic circulation BNP levels were markedly elevated in the presence of cardiogenic/circulatory shock [37]. Besides, cord blood BNP was significantly higher in infants with hypotension and cardiac dysfunction treated with dopamine than in infants without

dopamine administration. A cutoff values of >90 pg/L yielded a sensitivity of 68% and specificity of 84%, for identifying neonates who required dopamine administration after birth [38].

Concerning NTproBNP, their levels in the cord blood were higher in neonates with CHD [39,40] and this was especially evident in the right ventricular outflow tract obstruction without ventricular septal defect group. Additionally, elevated NTproBNP levels were indicators of functional single ventricle (substantially increased) and in neonates with CHD it was noted a marked increase of their levels in the first week of life [40]. A study with a 1-year follow-up showed that cord blood NTproBNP was associated with 1-year survival [39].

NTproBNP correlated with echocardiography measurements, namely LA/Ao ratio and a less significant negative correlation between NTproBNP and left ventricular function [41].

A study concerning cardiac neonatal lupus showed that median cord blood NTproBNP levels were higher in cardiac neonatal lupus cases than in unaffected fetuses and positively associated in a multivariate analysis ($p=0.04$) including as covariates maternal IV Ig/hydroxychloroquine, steroid exposure at birth and week of delivery [42].

BNP/NTproBNP in pulmonary hypertension

A study demonstrated a positive correlation between mean pulmonary artery pressure and BNP levels ($r=0.643$, $p<0.0001$) [43] . BNP values were higher in infants with persistent pulmonary hypertension (PH) relative to controls (neonates with non-cardiac causes of respiratory distress (RD) and neonates without RD). BNP levels correlated with echocardiographic parameters of PH such as the gradient of the tricuspid regurgitation jet and the ratio of tricuspid regurgitation jet gradient to mean blood pressure [44]. In infants with persistent PH with criteria for inhaled NO (iNO) therapy, initial BNP levels above 30 ng/dL showed excellent sensitivity 100% and negative predictive value 10% for predicting the subsequent need for iNO [45]

For NTproBNP, a correlation to estimated pulmonary mean pressure ($r=0.45$; $p=0.03$) and to the diastolic impairment signs of PH in the echocardiography: global right ventricle function (RV Tei index) and tricuspid E/A ratio was also found [46]. In term neonates with RD,PH was associated with significantly higher NTproBNP ($p<0.001$), irrespective of its etiology: CHD or pulmonary disease [47]. Moreover, in neonates with PH, early elevations in NTproBNP levels were observed in non-survivors, significantly higher than survivors [46].

BNP/NTproBNP in Respiratory Distress, Bronchopulmonary Dysplasia and Transient Tachypnea of the Newborn

In infants with RD, the median BNP concentration was significantly elevated in the ones with CHD compared to non-CHD group ($p<0.001$) and showed to have a good sensitivity and negative predictive value to exclude serious cardiovascular problems in neonates with RD. However, not all CHD were associated with ventricular stress and raised BNP levels [48]

Concerning NTproBNP, neonates with RD had significantly higher NTproBNP ($p<0.04$) [41,47], showing a different time course according to the underlying disease. On the first day of life, NTproBNP could not differentiate according to the underlying disease but from the second day of life onwards, NTproBNP enabled differentiation between CHD or other than cardiac reasons (respiratory disorder or perinatal asphyxia) [49]. In opposition, a study with term neonates with RD, NTproBNP levels were not significantly different according to the etiology: CHD or pulmonary disease [47].

About Bronchopulmonary Dysplasia (BPD), BNP is significantly higher in preterm infants with this condition and it correlates with BPD severity: significantly elevated in severe BPD compared to moderate and mild BPD ($p<0.001$) [50].

NTproBNP levels were also more elevated in newborns with RD who developed BPD and in the non-survivors ones ($p<0.001$). These findings were demonstrated in both infants with a diagnosis of PDA ($p<0.001$) and in infants without ($p<0.05$) [51] . Accordingly, in preterm who developed BPD, NTproBNP concentrations were significantly higher than preterm without BPD and healthy term. Concentration of NTproBNP positively correlated with severity of RD, independently with BDP only, while taking into account 5-minute Apgar scores, gestational age and birth weight as potential confounders ($p<0.002$) [52].

Regarding **t**ransient tachypnea of the newborn (TTN), a study in 2012, noted that the mean NTproBNP concentrations in neonates with TTN were significantly higher than in controls at the 6th, 24th, 72th and 120th of life ($p<0.001$) and there was a moderate correlation between concentrations at 24 hours and duration of tachypnea (r: 0.41, p=0.001). Moreover, a cutoff value of >6575 pg/ml NTproBNP at 24 h showed a sensitivity of 85% and specificity of 64% to predict mechanical ventilation support [53]. One year after, a more recent study, showed that the average of NTproBNP levels did not differ significantly between the study group with TTN and controls [54]. No studies were found aiming BNP in TTN.

Troponin I/T

Troponin I/T in Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy

Several studies showed that TnT levels were more elevated in infants with perinatal asphyxia compared to controls, in the cord blood ($p<0.01$) and at 3rd, 6th, 12th, 24th and 48th hours ($p<0.001$) [55-61]. The periods when specificity and sensitivity were highest together were the 12th and 24th hours [55]. These values decreased at 48th and 72th hours[57]. TnI values were also significantly higher in infants with perinatal asphyxia [62,63] correlating positively with the traditional markers of asphyxia as arterial umbilical pH and bicarbonate, base deficit and Apgar score [62]. This correlation was not present at 12 hours of life [63].

A Nigerian study with negroid neonates also showed TnT levels significantly higher in asphyxiated infants but significantly higher in deliveries assisted by vacuum or forceps, contrasting with studies in developed countries where TnT levels were not affected by mode of delivery [64].

In neonates with moderate to severe asphyxia TnT levels were significantly higher in the presence of myocardial injury [58,65,66] with levels being higher in severe asphyxia compared to mild and no asphyxia [57,58,67]. On day 3 and 7, TnT levels remained high in neonates with severe perinatal asphyxia [67]. No significant difference was detected between neonates with mild asphyxia and controls [57].

TnT levels correlated with echocardiographic findings of myocardial dysfunction [56,57,66] as it correlated positively with the left and right ventricle Tei index [56], stroke volume and left ventricular output [66] and negatively with the mitral and tricuspid systolic (Sm) velocity [56]. Systolic and diastolic functions were generally preserved in asphyxiated infants but the reduction of the left ventricular output and stroke volume suggested a sub clinical myocardial injury [66].

Moreover, TnT levels were significantly higher in hypotensive neonates needing inotropic support/catecholamine [56,61], in the ones who develop congestive cardiac failure [60] and in the non survivors [25,56,58,60], with a cutoff of 0.15 µg/l, giving a specificity of 100% and a sensitivity of 70% to predict mortality [56].

Several studies also showed that infants with perinatal asphyxia who developed hypoxic ischemic encephalopathy (HIE) had raised TnI levels with increasing severity of HIE, being strongly correlated with its clinical grade [38,68,69]. TnI concentrations at 36 h of life correlated strongly with duration of inotropic support [68] and the non-survivors had significantly high raised levels of TnI in comparison to survivors [38,68,69]. A cord blood level of 4.6 ng/ml was found to be the optimal cutoff level in predicting early mortality with a sensitivity: 77% and specificity: 97%, showing a higher specificity, positive predictive value and AUC than arterial umbilical base deficit and 5 minute Apgar [69].

Troponin I/T and Cardiac Dysfunction

Studies showed that TnT is as a marker of myocardial contractility reflecting the degree of myocardial compromise as it correlates with echocardiographic markers of myocardial function and stroke volume [41,66,70]. No correlation was found with left and right ventricular output [41].

A study with infants of diabetic mothers, TnI levels were significantly higher in left ventricular dysfunction and/or hypertrophic cardiomyopathy being as sensitive as echocardiographic measurements in the detection of cardiac dysfunction [71].

In a study with extremely low birth weight infants, TnT levels were higher in the ones with cardiac dysfunction who needed inotropic support for persistent hypotension in the first 48h after birth. The authors suggested that these values, in cord blood or in the first hours of life, could be an indicator to early cardiovascular support before clinical signs of hypotension appear [72].

Troponin I/T in Congenital Heart Defects

TnT concentrations in neonates with CHD were significantly higher than healthy controls. However, there was no correlation between its levels and clinical signs of heart failure, echocardiographic markers of left ventricular compromise or type of heart defect. TnT levels correlated positively with the hemodynamic significance of CHD ($p=0.048$) [73].

In a study with infants undergoing cardiac surgery for CHD, preoperative TnI was elevated in all neonates undergoing cardiac surgery with cardiopulmonary bypass: hypoplastic left-heart syndromes and transpositions of the great arteries, with or without ventricular sept defect compared to controls: Blalock-Taussig shunt and coarctation of aorta [74]. In opposition, a study also with TnI did not find significant differences between healthy and CHD groups or between groups of CHD, neither between the need of conservative versus surgical treatment [75].

Troponin I/T in Patent Ductus Arteriosus

Studies showed that TnT levels at the 48th of life were significantly higher in preterm with persistent PDA compared to those with spontaneous closure ($p<0.001$) [25,76]. A significant correlation was found between TnT levels and echocardiographic parameters: ductal diameter, LA/Ao ratio, and descending aortic end-diastolic velocity. A cutoff of 0.20 µg/L yielded a sensitivity of 70% and a specificity of 75% to diagnose PDA. Following successful treatment, TnT levels decreased significantly ($p<.001$) [76]. In opposition, another study, found no correlation between PDA LA/Ao ratio and TnT [41]. As NTproBNP, TnT levels were significantly higher in a PDA that could later develop severe intraventricular hemorrhage or death compared to a PDA without complications [25]. No studies were found concerning TnI and PDA.

Troponin I/T in Respiratory Distress

Several studies showed that newborns with RD had significantly higher TnT ($p<0.01$) compared to controls [41,59,70,77-80] and these concentrations were positively correlated to oxygen requirement [78], duration of ventilatory support [77] and to the need of inotropic support [70,78]. In addition, the infants who later died tended to have higher TnT levels than the ones who survived [78,80].

Accordingly, in a study with ventilated infants with idiopathic moderate to severe RD syndrome they had significantly higher TnI levels than healthy infants ($p<0.05$), with the ones with severe RD showing higher TnI levels than moderate RD ones ($p<0.05$) [81].

CKMB

CKMB in Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy

Several studies demonstrated that CKMB levels in neonates with perinatal asphyxia were significantly higher in the cord and venous blood samples when compared to controls [55,59,62,67]. Specificity for cardiac damages increased from 50% in the cord blood to 96% at 24 hours, whereas sensitivity decreased from 86% in the cord blood to 40% at 24 hours. A positive correlation was found between the TnT and CKMB values at the 6th and 12th hour, however, no correlation could be found at the 3rd and 24th hour [55]. The best cutoff found for CKMB in a study had lesser sensitivity and specificity than TnT to predict myocardial damage but more value than echocardiographic examination [59]. CKMB levels also correlated with severity, being significantly higher in asphyxia grade II and III than grade I and healthy controls within the first 2 to 4 hours. These differences were not found on day 3 [67].

In infants with asphyxia, CKMB concentrations are elevated in the presence of myocardial injury, acute kidney injury or both [65].

In term infants with perinatal asphyxia who later developed to HIE, CKBM levels were raised but with less sensitivity and specificity than TnI [38,62,69] and no relationship with cardiac dysfunction, severity and mortality [38,69]. Also, CKMB had a correlation with mode of delivery, gestational age and birth weight [62].

CKMB in Congenital Heart Defect

There was no significant difference in CKMB levels between healthy and CHD neonates or between groups of CHD. However levels of CKMB were elevated in patients with CHD who had surgery correction in the hospitalized neonatal period than in those discharged without surgery ($p<0.05$) with a

cutoff of >4.6 ng/mL demonstrating a sensitivity of 87.5% and specificity of 63.6% for predicting surgery. Moreover, CKMB correlated negatively with echocardiographic measurements of diastolic function as mitral valve lateral annulus peak early/late diastolic velocity ratio [75].

Myoglobin

Myoglobin in Congenital Heart Defect

Myoglobin levels were not significantly different between healthy and CHD groups or between groups of CHD, neither between conservative treatment or surgical groups with CHD [75].

Synthesis of results

The synthesis of the results stated above are summarized in table 3.

Studies showed significantly higher levels of BNP/NTproBNP in PDA [15,16,25], CHD [35,36,39], PH [43,46], RD [41,47,48] and BPD [50-52]. In TTN, different studies showed opposing results [53,54].

BNP/NTproBNP in PDA correlated with echo measurements [15,20,21,25,26,29-31], the presence and severity of an hsPDA [19-21,26-29], the need for treatment [23,24,27,30] with decreasing levels after successful closure [15,19,27,32], complications and mortality [25]. Different cutoffs could be used to determine hsPDA (table 2) for both BNP and NTproBNP as their role seem to me similarly useful [34].

BNP/NTproBNP in critical CHD infants with ductal-dependent systemic circulation were markedly elevated in the presence of cardiogenic/circulatory shock [37] and could be used for detecting infants who required dopamine administration in the first hours of life [38].

In PH, BNP/NTproBNP concentrations correlated with echocardiographic parameters of PH [43,44] and to the diastolic impairment associated [46]. In a study with infants with persistent PH, BNP showed good sensitivity and negative predictive value for predicting the subsequent iNO requirement [45]. NTproBNP correlated also with mortality [46].

About BNP/NTproBNP in RD, studies showed different results in the role of this biomarker to identify the etiology of the RD, despite its good sensitivity and negative predictive value to exclude serious cardiovascular problems. NP/NTproBNP levels correlated with BPD severity and mortality [50-52].

Studies concerning TnI/T demonstrated its higher concentrations in perinatal asphyxia and HIE[55-61] [62,63], Cardiac dysfunction [41,66,70,71], CHD (only TnT) [73,74], PDA (only TnT) [25,76] and RD [41,59,70,77-80].

In perinatal asphyxia, TnI/T levels correlated with echocardiographic findings of myocardial dysfunction [56,57,66], severity [57,58,67], congestive heart failure [60], the need of inotropic support/catecholamine [56,61] and mortality [25,56,58,60]. Neonates with perinatal asphyxia who developed HIE had raised TnI levels, correlated also with severity of HIE, its clinical grade and mortality [38,68,69].

TnT in CHD despite its high levels, there was no correlation between its levels and clinical signs of heart failure, echocardiographic markers of left ventricular compromise or type of heart defect [73]. Studies with TnI in CHD showed opposing results [74,75].

In PDA, studies focusing on TnT showed different results concerning its correlation with echocardiographic measurements [41,76] but a positive correlation with complications and mortality [25]. No studies were found concerning TnI and PDA.

TnT in RD correlated with oxygen requirement [78], duration of ventilatory support [77], the need of inotropic support [70,78] and mortality [78,80], as TnI correlated with RD severity [81].

Regarding CKMB, studies demonstrated its high levels in perinatal asphyxia and HIE [38,55,59,62,67,69] and CHD [75].

CKMB in perinatal asphyxia correlated with echocardiographic findings of myocardial injury and severity but with lesser sensitivity and specificity than TnT to predict myocardial damage as it is influenced by several factors such as the presence of kidney injury, mode of delivery, gestational age and birth weight [62,65]. In HIE, CKMB had no relationship with cardiac dysfunction, severity and mortality [38,69].

In CHD, there was no significant difference in CKMB levels between controls and CHD neonates but its levels were higher in neonates with CHD who had surgery correction in the hospitalized neonatal period than in those discharged without surgery [75].

About Myoglobin, there was only one study found with no relevant results in CHD. Their values showed no significant difference between healthy and CHD groups or between groups of CHD, neither between conservative treatment or surgical groups with CHD.

Limitations of individual studies

Different studies addressed in this article find similar limitations in their study design, namely concerning the low number of the population studied and the difficulty to find a group of healthy neonates, especially if they only consider preterm. Besides, the quantity of blood for analysis must to be the least possible, differing from test to test and making it hard to evaluate the evolution of some biomarkers across time. Other mentioned limitation was the vascular accesses difficulty in some neonates with less birth weight or with a life-threatening condition that had to be prioritized.

Discussion

Summary of evidence

Main studies concerning BNP/NTproBNP centered its role in PDA. Evidence show that due to the good correlation between NTproBNP/BNP levels and echocardiographic PDA parameters, these peptides represent a useful diagnostic tool, with good sensitivity and specificity, in the diagnosis of an hsPDA. These levels can be used to guide physicians to consider early echocardiographic evaluation or in its absence to transfer the newborn to a proper place with pediatric cardiology facilities. Using certain cutoffs, it could be possible to identify the ones who require an early and individualized therapy. In the other hand, low levels may aid in the recognition of neonates with a closed ductus or a PDA that would most likely close spontaneously, reducing overtreatment. In addition, as its levels decreases with ductal closure, NTproBNP/BNP can be useful for monitoring efficacy of treatment. The considerably variation of the different cutoff values to diagnose hsPDA, was a consequence of the different assay methods (not addressed in this study) and to the time of the blood sampling.

The evidence does not define a role for BNP/NTproBNP in CHD, as not all defects are associated with ventricular stress and elevated BNP/NTproBNP values.

Concerning PH, despite its good correlation to echocardiographic findings, BNP/NTproBNP clinical relevance needs further studies. In combination with other clinical and laboratory information, these markers could be used to help diagnose persistent PH, especially in a care facility with limited access to pediatric echocardiography and as a guide for early pulmonary vasodilator therapy or even transfer to an extracorporeal membrane oxygenation center in newborns with more serious disease and worse prognosis.

In RD, BNP/NTproBNP demonstrated its greater importance in BPD. Its levels are higher in BPD with strongest correlation in neonates with PDA but also in newborns with no PDA and evidence also show correlation with clinical severity of respiratory disease. These findings suggest that using this biomarker could help in a better diagnosis and management of myocardial sequela of BPD.

Evidence demonstrate that TnI/T level is a useful tool for showing cardiac damage in neonates with perinatal asphyxia. Its sensitivity and specificity are much higher than echocardiography and other biomarkers such as CKMB, while the implementation of the method is simple. Moreover, it is a reliable indicator of severity and mortality. This early detection of myocardial damage could improve the management and survival of these infants, providing proper cardiovascular support besides managing the primary condition.

TnI/T, though it has high concentrations in CHD, it is independent of the type of heart defect and there is no correlation between its levels and clinical signs of heart failure or echocardiographic markers of left ventricular compromise. It may be useful as a marker of myocardial contractility. Further studies are required to explore its application. In PDA in particular, TnT may be valuable in evaluating ductal significance and response to therapy, due to its correlation with echocardiographic flow patterns. These raised levels may reflect the potential cardiac injury caused by a PDA and TnT measurements may identify infants at risk for PDA associated myocardial ischemia that would benefit from early treatment. In fact, evidence show that BNP/NTproBNP and TnT in addition to echocardiographic findings may guide future

trials of targeted medical treatment in neonates with a PDA, namely neonates with higher risk of severe complication who may benefit from an early and individualized therapy.

Regarding TnT in RD, evidence show that this biomarker is also a useful and specific marker for myocardial injury in newborns with RD. Its concentrations could be used to guide treatment and manage the evolution of this condition, as it correlates with severity and mortality.

CKMB as referred above does not seem to be specific enough to be of clinical value, being less specific and sensitive for myocardial injury than TnI/T.

Myoglobin is the least studied cardiac biomarker with only one article meeting the criteria for this revision.

Limitations

Although it is a systematic review, it is still difficult to locate all the studies concerning the subject. Only PubMed was used as a database and despite our best efforts, some articles were not assessed, once we did not have access to full text. Besides, some studies with pediatric populations included neonates but they did not perform analysis in a group only with neonates, being excluded.

Conclusions

Cardiac Biomarkers are a useful and fast diagnostic tool that have great potential in the management of neonatal patients and for becoming as important as other diagnostic tests in pathologies of the heart. BNP/NTproBNP and TnI/T seem to be the ones with greater value.

BNP/NTproBNP can be used in the diagnosis and management of PDA, as it has a good correlation with diagnosis, treatment and prognosis. The cutoff for diagnosing hsPDA must be established according to the type of biomarker, gestational age and assay method. TnT may be a beneficial additional marker for this disease, correlating with ductal significance and treatment response. Moreover, BNP/NTproBNP can play a significant role, with other clinical and laboratory findings, in the diagnosis of PH and as guide for treatment in this condition and in the diagnosis and management of myocardial sequela in BPD.

TnI/T finds its clinical relevance in perinatal asphyxia as a marker of myocardial injury and a reliable indicator of severity and mortality.

Further studies with larger cohort populations are needed for stablishing the right cutoff values specific for each neonatal pathology allowing its early and proper management.

Author Disclosures

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Compliance with Ethical Standards

Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

1. Bettencourt P (2004) NT-proBNP and BNP: biomarkers for heart failure management. Eur J Heart Fail 6 (3):359-363. doi:10.1016/j.ejheart.2004.01.008

2. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R, Jr. (1999) National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 45 (7):1104-1121

3. Cantinotti M, Clerico A, Murzi M, Vittorini S, Emdin M (2008) Clinical relevance of measurement of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide in pediatric cardiology. Clin Chim Acta 390 (1-2):12-22. doi:10.1016/j.cca.2007.12.020

4. Correale M, Nunno L, Ieva R, Rinaldi M, Maffei G, Magaldi R, Di Biase M (2009) Troponin in newborns and pediatric patients. Cardiovasc Hematol Agents Med Chem 7 (4):270-278

5. Daniels LB, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50 (25):2357-2368. doi:10.1016/j.jacc.2007.09.021

6. Witthaut R (2004) Science review: natriuretic peptides in critical illness. Crit Care 8 (5):342-349. doi:10.1186/cc2890

7. Soldin SJ, Soldin OP, Boyajian AJ, Taskier MS (2006) Pediatric brain natriuretic peptide and N-terminal pro-brain natriuretic peptide reference intervals. Clin Chim Acta 366 (1-2):304-308. doi:10.1016/j.cca.2005.11.005

8. El-Khuffash AF, Molloy EJ (2008) Serum troponin in neonatal intensive care. Neonatology 94 (1):1-7. doi:10.1159/000112540

9. Filatov VL, Katrukha AG, Bulargina TV, Gusev NB (1999) Troponin: structure, properties, and mechanism of functioning. Biochemistry (Mosc) 64 (9):969-985

10. Eerola A, Poutanen T, Savukoski T, Pettersson K, Sairanen H, Jokinen E, Pihkala J (2014) Cardiac troponin I, cardiac troponin-specific autoantibodies and natriuretic peptides in children with hypoplastic left heart syndrome. Interact Cardiovasc Thorac Surg 18 (1):80-85. doi:10.1093/icvts/ivt430

11. Danese E, Montagnana M (2016) An historical approach to the diagnostic biomarkers of acute coronary syndrome. Ann Transl Med 4 (10):194. doi:10.21037/atm.2016.05.19

12. Sarko J, Pollack CV, Jr. (2002) Cardiac troponins. J Emerg Med 23 (1):57-65

13. Sobki SH, Saadeddin SM, Habbab MA (2000) Cardiac markers used in the detection of myocardial injury. Saudi Med J 21 (9):843-846

14. Eggers KM, Oldgren J, Nordenskjold A, Lindahl B (2004) Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. Am Heart J 148 (4):574-581. doi:10.1016/j.ahj.2004.04.030

15. Puddy VF, Amirmansour C, Williams AF, Singer DR (2002) Plasma brain natriuretic peptide as a predictor of haemodynamically significant patent ductus arteriosus in preterm infants. Clin Sci (Lond) 103 (1):75-77. doi:10.1042/

16. Mannarino S, Garofoli F, Mongini E, Cerbo RM, Codazzi AC, Tzialla C, Mazzucchelli I, Perotti G, Tinelli C, De Silvestri A, Manzoni P, Stronati M (2010) BNP concentrations and cardiovascular adaptation in preterm and fullterm newborn infants. Early Hum Dev 86 (5):295-298. doi:10.1016/j.earlhumdev.2010.04.003

17. da Graca RL, Hassinger DC, Flynn PA, Sison CP, Nesin M, Auld PA (2006) Longitudinal changes of brain-type natriuretic peptide in preterm neonates. Pediatrics 117 (6):2183-2189. doi:10.1542/peds.2005-1387

18. Flynn PA, da Graca RL, Auld PA, Nesin M, Kleinman CS (2005) The use of a bedside assay for plasma B-type natriuretic peptide as a biomarker in the management of patent ductus arteriosus in premature neonates. J Pediatr 147 (1):38-42. doi:10.1016/j.jpeds.2005.03.040

19. Sanjeev S, Pettersen M, Lua J, Thomas R, Shankaran S, L'Ecuyer T (2005) Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus arteriosus in preterm neonates. J Perinatol 25 (11):709-713. doi:10.1038/sj.jp.7211383

20. Choi BM, Lee KH, Eun BL, Yoo KH, Hong YS, Son CS, Lee JW (2005) Utility of rapid B-type natriuretic peptide assay for diagnosis of symptomatic patent ductus arteriosus in preterm infants. Pediatrics 115 (3):e255-261. doi:10.1542/peds.2004-1837

21. Lee JH, Shin JH, Park KH, Rhie YJ, Park MS, Choi BM (2013) Can early B-type natriuretic peptide assays predict symptomatic patent ductus arteriosus in extremely low birth weight infants? Neonatology 103 (2):118-122. doi:10.1159/000343034

22. Davlouros PA, Karatza AA, Xanthopoulou I, Dimitriou G, Georgiopoulou A, Mantagos S, Alexopoulos D (2011) Diagnostic role of plasma BNP levels in neonates with signs of congenital heart disease. Int J Cardiol 147 (1):42-46. doi:10.1016/j.ijcard.2009.07.029

23. Czernik C, Lemmer J, Metze B, Koehne PS, Mueller C, Obladen M (2008) B-type natriuretic peptide to predict ductus intervention in infants <28 weeks. Pediatr Res 64 (3):286-290. doi:10.1203/PDR.0b013e3181799594

24. Mine K, Ohashi A, Tsuji S, Nakashima J, Hirabayashi M, Kaneko K (2013) B-type natriuretic peptide for assessment of haemodynamically significant patent ductus arteriosus in premature infants. Acta Paediatr 102 (8):e347-352. doi:10.1111/apa.12273

25. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ (2008) Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed 93 (6):F407-412. doi:10.1136/adc.2007.133140

26. Occhipinti F, De Carolis MP, De Rosa G, Bersani I, Lacerenza S, Cota F, Rubortone SA, Romagnoli C (2014) Correlation analysis between echocardiographic flow pattern and N-terminal-pro-brain natriuretic peptide for early targeted treatment of patent ductus arteriosus. J Matern Fetal Neonatal Med 27 (17):1800-1804. doi:10.3109/14767058.2014.880879

27. Ramakrishnan S, Heung YM, Round J, Morris TP, Collinson P, Williams AF (2009) Early N-terminal pro-brain natriuretic peptide measurements predict clinically significant ductus arteriosus in preterm infants. Acta Paediatr 98 (8):1254-1259. doi:10.1111/j.1651-2227.2009.01315.x

28. Farombi-Oghuvbu I, Matthews T, Mayne PD, Guerin H, Corcoran JD (2008) N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed 93 (4):F257-260. doi:10.1136/adc.2007.120691

29. Kalra VK, DeBari VA, Zauk A, Kataria P, Myridakis D, Kiblawi F (2011) Point-of-care testing for B-type natriuretic peptide in premature neonates with patent ductus arteriosus. Ann Clin Lab Sci 41 (2):131-137

30. Martinovici D, Vanden Eijnden S, Unger P, Najem B, Gulbis B, Marechal Y (2011) Early NT-proBNP is able to predict spontaneous closure of patent ductus arteriosus in preterm neonates, but not the need of its treatment. Pediatr Cardiol 32 (7):953-957. doi:10.1007/s00246-011-0020-y

31. Letzner J, Berger F, Schwabe S, Benzing J, Morgenthaler NG, Bucher HU, Buhrer C, Arlettaz R, Wellmann S (2012) Plasma C-terminal pro-endothelin-1 and the natriuretic pro-peptides NT-proBNP and MR-proANP in very preterm infants with patent ductus arteriosus. Neonatology 101 (2):116-124. doi:10.1159/000330411

32. Nuntnarumit P, Khositseth A, Thanomsingh P (2009) N-terminal probrain natriuretic peptide and patent ductus arteriosus in preterm infants. J Perinatol 29 (2):137-142. doi:10.1038/jp.2008.185

33. Nuntnarumit P, Chongkongkiat P, Khositseth A (2011) N-terminal-pro-brain natriuretic peptide: a guide for early targeted indomethacin therapy for patent ductus arteriosus in preterm Infants. Acta Paediatr 100 (9):1217-1221. doi:10.1111/j.1651-2227.2011.02304.x

34. Konig K, Guy KJ, Drew SM, Barfield CP (2015) B-type and N-terminal pro-B-type natriuretic peptides are equally useful in assessing patent ductus arteriosus in very preterm infants. Acta Paediatr 104 (4):e139-142. doi:10.1111/apa.12892

35. Cantinotti M, Passino C, Storti S, Ripoli A, Zyw L, Clerico A (2011) Clinical relevance of time course of BNP levels in neonates with congenital heart diseases. Clin Chim Acta 412 (23-24):2300-2304. doi:10.1016/j.cca.2011.08.030

36. Cantinotti M, Storti S, Lorenzoni V, Murzi B, Marotta M, Crocetti M, Molinaro S, Assanta N, Lopez L, Clerico A (2013) Response of cardiac endocrine function to surgery stress is age dependent in neonates and children with congenital heart defects: consequences in diagnostic and prognostic accuracy of brain natriuretic peptide measurement. Pediatr Crit Care Med 14 (5):508-517. doi:10.1097/PCC.0b013e31828a89b9

37. Das S, Chanani NK, Deshpande S, Maher KO (2012) B-type natriuretic peptide in the recognition of critical congenital heart disease in the newborn infant. Pediatr Emerg Care 28 (8):735-738. doi:10.1097/PEC.0b013e3182624a12

38. Agrawal J, Shah GS, Poudel P, Baral N, Agrawal A, Mishra OP (2012) Electrocardiographic and enzymatic correlations with outcome in neonates with hypoxic-ischemic encephalopathy. Ital J Pediatr 38:33. doi:10.1186/1824-7288-38-33

39. Bae JY, Cha HH, Seong WJ (2015) Amino-Terminal proB-Type Natriuretic Peptide Levels in the Umbilical Cord Blood of Neonates Differ According to the Type of Prenatally Diagnosed Congenital Heart Disease. Pediatr Cardiol 36 (8):1742-1747. doi:10.1007/s00246-015-1228-z

40. Lechner E, Wiesinger-Eidenberger G, Wagner O, Weissensteiner M, Schreier-Lechner E, Leibetseder D, Arzt W, Tulzer G (2009) Amino terminal pro B-type natriuretic peptide levels are elevated in the cord blood of neonates with congenital heart defect. Pediatr Res 66 (4):466-469. doi:10.1203/PDR.0b013e3181b3aee4

41. El-Khuffash A, Davis PG, Walsh K, Molloy EJ (2008) Cardiac troponin T and N-terminal-pro-B type natriuretic peptide reflect myocardial function in preterm infants. J Perinatol 28 (7):482-486. doi:10.1038/jp.2008.21

42. Saxena A, Izmirly PM, Han SW, Briassouli P, Rivera TL, Zhong H, Friedman DM, Clancy RM, Buyon JP (2015) Serum Biomarkers of Inflammation, Fibrosis, and Cardiac Function in Facilitating Diagnosis, Prognosis, and Treatment of Anti-SSA/Ro-Associated Cardiac Neonatal Lupus. J Am Coll Cardiol 66 (8):930-939. doi:10.1016/j.jacc.2015.06.1088

43. Ikemoto Y, Nogi S, Teraguchi M, Kojima T, Hirata Y, Kobayashi Y (1996) Early changes in plasma brain and atrial natriuretic peptides in premature infants: correlation with pulmonary arterial pressure. Early Hum Dev 46 (1-2):55-62

44. Reynolds EW, Ellington JG, Vranicar M, Bada HS (2004) Brain-type natriuretic peptide in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatrics 114 (5):1297-1304. doi:10.1542/peds.2004-0525

45. Shah N, Natarajan G, Aggarwal S (2015) B-type natriuretic peptide: biomarker of persistent pulmonary hypertension of the newborn? Am J Perinatol 32 (11):1045-1049. doi:10.1055/s-0035-1548540

46. Baptista MJ, Rocha G, Clemente F, Azevedo LF, Tibboel D, Leite-Moreira AF, Guimaraes H, Areias JC, Correia-Pinto J (2008) N-terminal-pro-B type natriuretic peptide as a useful tool to evaluate pulmonary hypertension and cardiac function in CDH infants. Neonatology 94 (1):22-30. doi:10.1159/000112641

47. Markovic-Sovtic G, Kosutic J, Jankovic B, Bojanin D, Sovtic A, Radojicic Z, Rakonjac MZ (2014) N-terminal pro-brain natriuretic peptide in the assessment of respiratory distress in term neonates. Pediatr Int 56 (3):373-377. doi:10.1111/ped.12258

48. Ko HK, Lee JH, Choi BM, Lee JH, Yoo KH, Son CS, Lee JW (2008) Utility of the rapid B-type natriuretic peptide assay for detection of cardiovascular problems in newborn infants with respiratory difficulties. Neonatology 94 (1):16-21. doi:10.1159/000112584

49. Lechner E, Weissensteiner M, Wagner O, Schreier-Lechner E, Rehak P, Prandstetter C, Furthner D, Wiesinger-Eidenberger G (2013) Aminoterminal pro-B-type natriuretic peptide: heart or lung disease in the neonate? Pediatr Crit Care Med 14 (4):396-402. doi:10.1097/PCC.0b013e3182772f98

50. Kalra VK, Aggarwal S, Arora P, Natarajan G (2014) B-type natriuretic peptide levels in preterm neonates with bronchopulmonary dysplasia: a marker of severity? Pediatr Pulmonol 49 (11):1106-1111. doi:10.1002/ppul.22942

51. Sellmer A, Hjortdal VE, Bjerre JV, Schmidt MR, McNamara PJ, Bech BH, Henriksen TB (2015) N-Terminal Pro-B Type Natriuretic Peptide as a Marker of Bronchopulmonary Dysplasia or Death in Very Preterm Neonates: A Cohort Study. PLoS One 10 (10):e0140079. doi:10.1371/journal.pone.0140079

52. Joseph L, Nir A, Hammerman C, Goldberg S, Ben Shalom E, Picard E (2010) N-terminal pro-B-type natriuretic peptide as a marker of bronchopulmonary dysplasia in premature infants. Am J Perinatol 27 (5):381-386. doi:10.1055/s-0029-1243312

53. Aydemir O, Aydemir C, Sarikabadayi YU, Altug N, Erdeve O, Uras N, Oguz SS, Dilmen U (2012) The role of plasma N-terminal pro-B-type natriuretic peptide in predicting the severity of transient tachypnea of the newborn. Early Hum Dev 88 (5):315-319. doi:10.1016/j.earlhumdev.2011.08.026

54. Kara S, Tonbul A, Karabel M, Akca H, Uras N, Tatli M (2013) The role of serum N-terminal pro-brain natriuretic peptide in transient tachypnea of the newborn. Eur Rev Med Pharmacol Sci 17 (13):1824-1829

55. Yildirim A, Ozgen F, Ucar B, Alatas O, Tekin N, Kilic Z (2016) The Diagnostic Value of Troponin T Level in the Determination of Cardiac Damage in Perinatal Asphyxia Newborns. Fetal Pediatr Pathol 35 (1):29-36. doi:10.3109/15513815.2015.1122128

56. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M (2010) Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. Pediatr Cardiol 31 (5):634-642. doi:10.1007/s00246-010-9661-5

57. Wei Y, Xu J, Xu T, Fan J, Tao S (2009) Left ventricular systolic function of newborns with asphyxia evaluated by tissue Doppler imaging. Pediatr Cardiol 30 (6):741-746. doi:10.1007/s00246-009-9421-6

58. Rajakumar PS, Bhat BV, Sridhar MG, Balachander J, Konar BC, Narayanan P, Chetan G (2008) Cardiac enzyme levels in myocardial dysfunction in newborns with perinatal asphyxia. Indian J Pediatr 75 (12):1223-1225. doi:10.1007/s12098-008-0242-z

59. Szymankiewicz M, Matuszczak-Wleklak M, Vidyasagar D, Gadzinowski J (2006) Retrospective diagnosis of hypoxic myocardial injury in premature newborns. J Perinat Med 34 (3):220-225. doi:10.1515/JPM.2006.040

60. Boo NY, Hafidz H, Nawawi HM, Cheah FC, Fadzil YJ, Abdul-Aziz BB, Ismail Z (2005) Comparison of serum cardiac troponin T and creatine kinase MB isoenzyme mass concentrations in asphyxiated term infants during the first 48 h of life. J Paediatr Child Health 41 (7):331-337. doi:10.1111/j.1440-1754.2005.00626.x

61. Szymankiewicz M, Matuszczak-Wleklak M, Hodgman JE, Gadzinowski J (2005) Usefulness of cardiac troponin T and echocardiography in the diagnosis of hypoxic myocardial injury of full-term neonates. Biol Neonate 88 (1):19-23. doi:10.1159/000084067

62. Turker G, Babaoglu K, Duman C, Gokalp A, Zengin E, Arisoy AE (2004) The effect of blood gas and Apgar score on cord blood cardiac troponin I. J Matern Fetal Neonatal Med 16 (5):315-319. doi:10.1080/14767050400017991

63. Trevisanuto D, Picco G, Golin R, Doglioni N, Altinier S, Zaninotto M, Zanardo V (2006) Cardiac troponin I in asphyxiated neonates. Biol Neonate 89 (3):190-193. doi:10.1159/000089795

64. Sadoh WE, Eregie CO (2012) Cardiac troponin T as a marker of myocardial injury in a group of asphyxiated African neonates. Paediatr Int Child Health 32 (1):43-46. doi:10.1179/1465328111Y.0000000046

65. Sadoh WE, Eregie CO, Nwaneri DU, Sadoh AE (2014) The diagnostic value of both troponin T and creatinine kinase isoenzyme (CK-MB) in detecting combined renal and myocardial injuries in asphyxiated infants. PLoS One 9 (3):e91338. doi:10.1371/journal.pone.0091338

66. Costa S, Zecca E, De Rosa G, De Luca D, Barbato G, Pardeo M, Romagnoli C (2007) Is serum troponin T a useful marker of myocardial damage in newborn infants with perinatal asphyxia? Acta Paediatr 96 (2):181-184

67. Gunes T, Ozturk MA, Koklu SM, Narin N, Koklu E (2005) Troponin-T levels in perinatally asphyxiated infants during the first 15 days of life. Acta Paediatr 94 (11):1638-1643. doi:10.1080/08035250510041222

68. Shastri AT, Samarasekara S, Muniraman H, Clarke P (2012) Cardiac troponin I concentrations in neonates with hypoxic-ischaemic encephalopathy. Acta Paediatr 101 (1):26-29. doi:10.1111/j.1651-2227.2011.02432.x

69. Turker G, Babaoglu K, Gokalp AS, Sarper N, Zengin E, Arisoy AE (2004) Cord blood cardiac troponin I as an early predictor of short-term outcome in perinatal hypoxia. Biol Neonate 86 (2):131-137. doi:10.1159/000079068

70. Clark SJ, Newland P, Yoxall CW, Subhedar NV (2006) Sequential cardiac troponin T following delivery and its relationship with myocardial performance in neonates with respiratory distress syndrome. Eur J Pediatr 165 (2):87-93. doi:10.1007/s00431-005-0001-3

71. Korraa A, Ezzat MH, Bastawy M, Aly H, El-Mazary AA, Abd El-Aziz L (2012) Cardiac troponin I levels and its relation to echocardiographic findings in infants of diabetic mothers. Ital J Pediatr 38:39. doi:10.1186/1824-7288-38-39

72. Cruz MA, Bremmer YA, Porter BO, Gullquist SD, Watterberg KL, Rozycki HJ (2006) Cardiac troponin T and cardiac dysfunction in extremely low-birth-weight infants. Pediatr Cardiol 27 (4):396-401. doi:10.1007/s00246-005-0942-3

73. Tarkowska A, Furmaga-Jablonska W (2012) The evaluation of diagnostic role of cardiac troponin T (cTnT) in newborns with heart defects. ScientificWorldJournal 2012:682538. doi:10.1100/2012/682538

74. Saraiya NR, Sun LS, Jonassen AE, Pesce MA, Queagebeur JM (2005) Serum cardiac troponin-I elevation in neonatal cardiac surgery is lesion-dependent. J Cardiothorac Vasc Anesth 19 (5):620-625. doi:10.1053/j.jvca.2005.07.004

75. Neves AL, Cabral M, Leite-Moreira A, Monterroso J, Ramalho C, Guimaraes H, Barros H, Guimaraes JT, Henriques-Coelho T, Areias JC (2016) Myocardial Injury Biomarkers in Newborns with Congenital Heart Disease. Pediatr Neonatol 57 (6):488-495. doi:10.1016/j.pedneo.2015.11.004

76. El-Khuffash AF, Molloy EJ (2008) Influence of a patent ductus arteriosus on cardiac troponin T levels in preterm infants. J Pediatr 153 (3):350-353. doi:10.1016/j.jpeds.2008.04.014

77. Awada H, Al-Tannir M, Ziade MF, Alameh J, El Rajab M (2007) Cardiac troponin T: a useful early marker for cardiac and respiratory dysfunction in neonates. Neonatology 92 (2):105-110. doi:10.1159/000100964

78. Clark SJ, Newland P, Yoxall CW, Subhedar NV (2004) Concentrations of cardiac troponin T in neonates with and without respiratory distress. Arch Dis Child Fetal Neonatal Ed 89 (4):F348-352. doi:10.1136/adc.2002.025478

79. Clark SJ, Newland P, Yoxall CW, Subhedar NV (2001) Cardiac troponin T in cord blood. Arch Dis Child Fetal Neonatal Ed 84 (1):F34-37

80. Trevisanuto D, Zaninotto M, Altinier S, Plebani M, Zanardo V (2000) High serum cardiac troponin T concentrations in preterm infants with respiratory distress syndrome. Acta Paediatr 89 (9):1134-1136

81. Distefano G, Sciacca P, Mattia C, Betta P, Falsaperla R, Romeo MG, Amato M (2006) Troponin I as a biomarker of cardiac injury in neonates with idiopathic respiratory distress. Am J Perinatol 23 (4):229-232. doi:10.1055/s-2006-939537

Table 1 *Studies characteristics*

Type of Study	Publication Date	City, Country	Population	Study Period	Main outcome	Reference
Observational	2004	London, UK	18 preterm <34weeks 11 healthy term controls	5 months	BNP in PDA	**[15]**
Observational	2010	Pavia, Italy	36 preterm <35weeks 34 healthy term	1 year 4 months	BNP in PDA	**[16]**
Prospective observational	2006	New York, USA	19 preterm <32 weeks	9 months	BNP in PDA	**[17]**
Observational	2005	New York, USA	20 preterm <36weeks	Not mentioned	BNP in PDA	**[18]**
Retrospective observational	2013	Seoul, Korea	73 extremely low birth weight	7 years 5 months	BNP in PDA	**[21]**
Prospective observational	2005	Detroit, USA	29 preterm <34weeks	11 months	BNP in PDA	**[19]**
Prospective observational	2005	Seoul, Korea	66 preterm <34weeks	1 year 3 months	BNP in PDA	**[20]**
Prospective observational	2011	Patras, Greece	75 neonates with suspected CHD	Not mentioned	BNP in LtR shunts and PDA	**[22]**
Prospective blinded clinical	2008	Berlin, Germany	67 preterm <28 weeks	1 year 8 months	BNP in PDA	**[23]**
Retrospective observational	2013	Osaka, Japan	46 preterm	2 years 9 months	BNP in PDA	**[24]**
Observational	2008	Dublin, Ireland	80 preterm <32weeks or <1500g	1 year 1 month	NTproBNP and TnT in PDA	**[25]**
Prospective observational	2014	Rome, Italy	41 preterm <32 weeks	1 year 8 months	NTproBNP in PDA	**[26]**
Blinded prospective	2009	London, UK	100 preterm <34weeks	2 years 1 month	NTproBNP in PDA	**[27]**
Prospective observational	2008	Dublin, Ireland	49 preterm <34 weeks	9 months	NTproBNP in PDA	**[28]**
Prospective observational	2011	New Jersey, USA	52 preterm <34 weeks or <1250g	1 year 1 month	BNP in PDA	**[29]**
Blinded prospective	2011	Brussels, Belgium	31 preterm <32 weeks or < 1500g	1 year	NTproBNP in PDA	**[30]**
Prospective, cross-sectional	2012	Zurich, Switzerland	218 neonates and infants with CHD 222 healthy age-matched controls	3 years	BNP in CHD	**[31]**
Observational	2009	Bangkok, Thailand	35 preterm <33 weeks	1 year 1 month	NTproBNP in PDA	**[32]**
Interventional	2011	Bangkok, Thailand	50 preterm <33 weeks	1 year	NTproBNP in PDA	**[33]**
Prospective observational	2015	Melbourne, Australia	58 preterm <32 weeks	Not mentioned	BNP and NTproBNP in PDA	**[34]**
Observational	2011	Massa, Italy	218 neonates and infants with CHD 222 healthy age-matched controls	3 years	BNP in CHD	**[35]**
Prospective observational	2013	Pisa, Italy	336 children with CHD (87 neonates) 436 healthy controls	2 years 4 months	BNP in CHD	**[36]**
Cohort	2012	Atlanta, USA	122 infants with ductal-dependent systemic circulation	4 years 5 months	BNP in CHD	**[37]**
Prospective observational	2012	Dharan, Nepal	60 term with perinatal asphyxia who developed to HIE	11 months	TnI and CKMB in HIE	**[38]**
Prospective observational	2015	Daegu, Korea	76 neonates with CHD 45 healthy controls	4 years 5 months	NTproBNP in CHD	**[39]**

Prospective observational	2009	Linz, Austria	60 neonates with CHD 200 control subjects	2 years 8 months	NTproBNP in CHD	**[40]**
Prospective observational	2008	Dublin, Ireland	80 neonates <1500g	11 months	TnT and NTproBNP in Cardiac Dysfunction	**[41]**
Cohort	2015	New York, USA	139 anti-SSA/Ro-exposed fetuses	Not mentioned	NTproBNP in cardiac neonatal lupus	**[42]**
Observational	1996	Tokyo, Japan	10 infants <36 weeks	1 year	BNP and pulmonary arterial pressure	**[43]**
Prospective cohort	2004	Lexington, USA	15 neonates with persistent PH 17 neonates with RD 15 healthy neonates	1 year	BNP in PH	**[44]**
Prospective observational	2015	Detroit, USA	19 term with persistent PH	Not mentioned	BNP in PH	**[45]**
Prospective observational	2008	Porto, Portugal	18 neonates with CHD 10 healthy age-matched controls	1 year 9 months	NTproBNP in PH	**[46]**
Prospective observational	2014	Belgrade, Serbia	62 neonates with RD	1 year 1 month	NTproBNP in RD	**[47]**
Prospective observational	2008	Seoul, Korea	73 term neonates with RD	1 year 8 months	BNP in RD	**[48]**
Prospective observational	2013	Linz, Austria	40 neonates with arterial duct-dependent CHD 40 neonates with RD without CHD	2 year 8 months	NTproBNP in RD	**[49]**
Prospective case-control observational	2014	Michigan, USA	60 preterm <32 weeks	Not mentioned	BNP in BPD	**[50]**
Cohort	2015	Aarhus, Denmark	134 preterm <32 weeks	1 year 8 months	NTproBNP in BPD	**[51]**
Prospective observational	2010	Jerusalem, Israel	34 preterm <34 weeks	1 year	NTproBNP in BPD	**[52]**
Prospective observational	2012	Ankara, Turkey	67 neonates with TTN 33 healthy controls	9 months	NTproBNP in TTN	**[53]**
Prospective observational	2013	Ankara, Turkey	87 neonates with CHD	1 year 1 month	BNP in TTN	**[54]**
Observational	2016	Eskisehir, Turkey	30 neonates with perinatal asphyxia 30 healthy controls	Not mentioned	TnT and CKMB in perinatal asphyxia	**[55]**
Prospective observational	2010	Mansoura, Egypt	25 neonates with perinatal asphyxia 20 healthy controls	1 year	TnT in perinatal asphyxia	**[56]**
Observational	2009	Zhejiang, China	31 neonates with severe perinatal asphyxia 31 neonates with mild perinatal asphyxia 30 healthy term	2 years 2 months	TnI in perinatal asphyxia	**[57]**
Prospective case-control observational	2008	Puducherry, India	30 term with perinatal asphyxia 30 healthy term controls	Not mentioned	TnT and CKMB in perinatal asphyxia	**[58]**
Retrospective observational	2006	Poznan, Poland	21 preterm with perinatal asphyxia 22 term controls	Not mentioned	TnT and CKMB in perinatal asphyxia and RD	**[59]**
Prospective observational	2005	Lumpur, Malasia	50 term with perinatal asphyxia 50 healthy term controls	2 years 2 months	TnT and CKMB in perinatal asphyxia	**[60]**
Observational	2005	Los Angeles, USA	39 term with perinatal asphyxia 44 healthy term controls	Not mentioned	TnT in perinatal asphyxia	**[61]**

Prospective observational	2004	Kocaeli, Turkey	112 neonates with perinatal asphyxia 84 healthy controls	2 years 3 months	TnI and CKMB in perinatal asphyxia and HIE	**[62]**
Observational	2006	Padova, Italy	13 neonates with perinatal asphyxia 39 healthy controls	2 years 5 months	TnI in perinatal asphyxia	**[63]**
Observational	2012	Benin, Nigeria	40 neonates with perinatal asphyxia 30 healthy controls	1 year	TnT in perinatal asphyxia	**[64]**
Observational	2014	Benin, Nigeria	40 neonates with moderate to severe perinatal asphyxia	1 year	TnT and CKMB in perinatal asphyxia	**[65]**
Prospective observational	2007	Rome, Italy	29 neonates with perinatal asphyxia 30 healthy controls	1 year	TnT in perinatal asphyxia	**[66]**
Prospective observational	2005	Kayseri, Turkey	45 neonates with perinatal asphyxia 15 healthy term controls	Not mentioned	TnT in perinatal asphyxia	**[67]**
Retrospective observational	2012	Norwich, UK	60 neonates with HIE	5 years	TnI in HIE	**[68]**
Prospective observational	2004	Kocaeli, Turkey	54 neonates with HIE 50 healthy controls	2 years 7 months	TnI in HIE	**[69]**
Prospective observational	2006	Liverpool, UK	24 neonates with RD 14 preterm without RD		TnT in RD	**[70]**
Prospective observational	2012	Cairo and Minia, Egypt	40 term of diabetic mothers 40 term of non-diabetic healthy mothers	3 years 2 months	TnI in Cardiac Dysfunction	**[71]**
Nested prospective cohort	2006	Richmond, USA	27 neonates (cardiovascular substudy of the PROPHET trial)	1 year 2 months	TnT in Cardiac Dysfunction	**[72]**
Observational	2012	Lublin, Poland	54 neonates with CHD 29 heathy neonates	Not mentioned	TnT in CHD	**[73]**
Prospective Cohort	2005	New York, USA	45 neonates with CHD	Not mentioned	TnI in CHD	**[74]**
Prospective observational	2016	Porto, Portugal	34 neonates with CHD 20 healthy controls	1 year 5 months	TnI, CKMB and Myoglobin in CHD	**[75]**
Observational	2008	Dublin, Ireland	80 preterm <1500g	Not mentioned	TnT in PDA	**[76]**
Prospective observational	2007	Beirut, Lebanon	48 neonates with RD 116 healthy controls	9 months	TnT in RD	**[77]**
Prospective observational	2004	Liverpool, UK	49 neonates with RD 113 healthy controls	1 year 1 month	TnT in RD	**[78]**
Observational	2001	Liverpool UK	27 neonates with RD 215 healthy controls	10 months	TnT in RD	**[79]**
Observational	2000	Padua, Italy	26 preterm <32 weeks with RD 20 preterm without RD	6 months	TnT in RD	**[80]**
Observational	2006	Catania, Italy	30 ventilated preterm with RD 10 healthy preterm	Not mentioned	TnI in RD	**[81]**

Tn: Troponin; PDA: patent ductus arteriosus; LtR shunts: left-to-right Shunts; CHD: congenital heart defect; PH: pulmonary hypertension; RD: respiratory distress; BPD: bronchopulmonary dysplasia; TTN: transient tachypnea of the newborn; HIE: hypoxic ischemic encephalopathy

Table 2 *Cutoffs proposed for hemodynamically significant patent ductus arteriosus*

Gestational age	Day	hsPDA/ included (*n*)	Proposed cutoff value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reference
<28 weeks	2	24/67	550pg/ml BNP (for ductus intervention)	0.86	83	76	77	90	[23]
<30 weeks	1	31/73	900 pg/ml BNP	0.83	54.8	95.2	89.5	74.1	[21]
<34 weeks	3	23/66	1110 pg/ml BNP	0.997	100	95.3	-	-	[20]
<34 weeks	3	17/52	123 ng/L BNP (for treatment)	1.00	100	100	-	-	[29]
<34 weeks	7 (mean)	14/29	70 pg/ml BNP	0.91	92.9	73.3	77	92	[19]
<36 weeks	2	20/20	300 pg/ml BNP (for PDA >1.5mm)	-	52	100	100	74	[18]
<37 weeks	2	16/34	283.5 pg/ml BNP	-	81.3	100			[22]
<42 weeks	2	19/75	201.5 pg/ml BNP	-	89.5	100	-	-	[22]
<32 weeks	1	29/46	<9854 pg/ml NTproBNP (for spontaneous closure)	0.86	71.8	100	-	-	[26]
<32 weeks	2	12/31	10 000 pg/ml NTproBNP (to exclude spontaneous closure)	0.92	89	100	100	87	[30]
<32 weeks	4	12/31	5000 pg/ml NTproBNP (to exclude spontaneous closure)	0.98	91	100	100	94	[30]
<33 weeks	2	12/35	10 180 pg/ml NTproBNP	0.964	100	91	86.7	100	[32]
<34 weeks	2	18/49	11 395 pg/ml NTproBNP	0.978	100	95	-	-	[28]
<34 weeks	3	20/56	2850 pmol/L NTproBNP (for clinically significant PDA)	-	90	89	82	90	[27]

hsPDA: hemodynamically significant patent ductus arteriosus; AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value

Table 3 *Cardiac Biomarkers in neonatal pathologies and their clinical relevance*

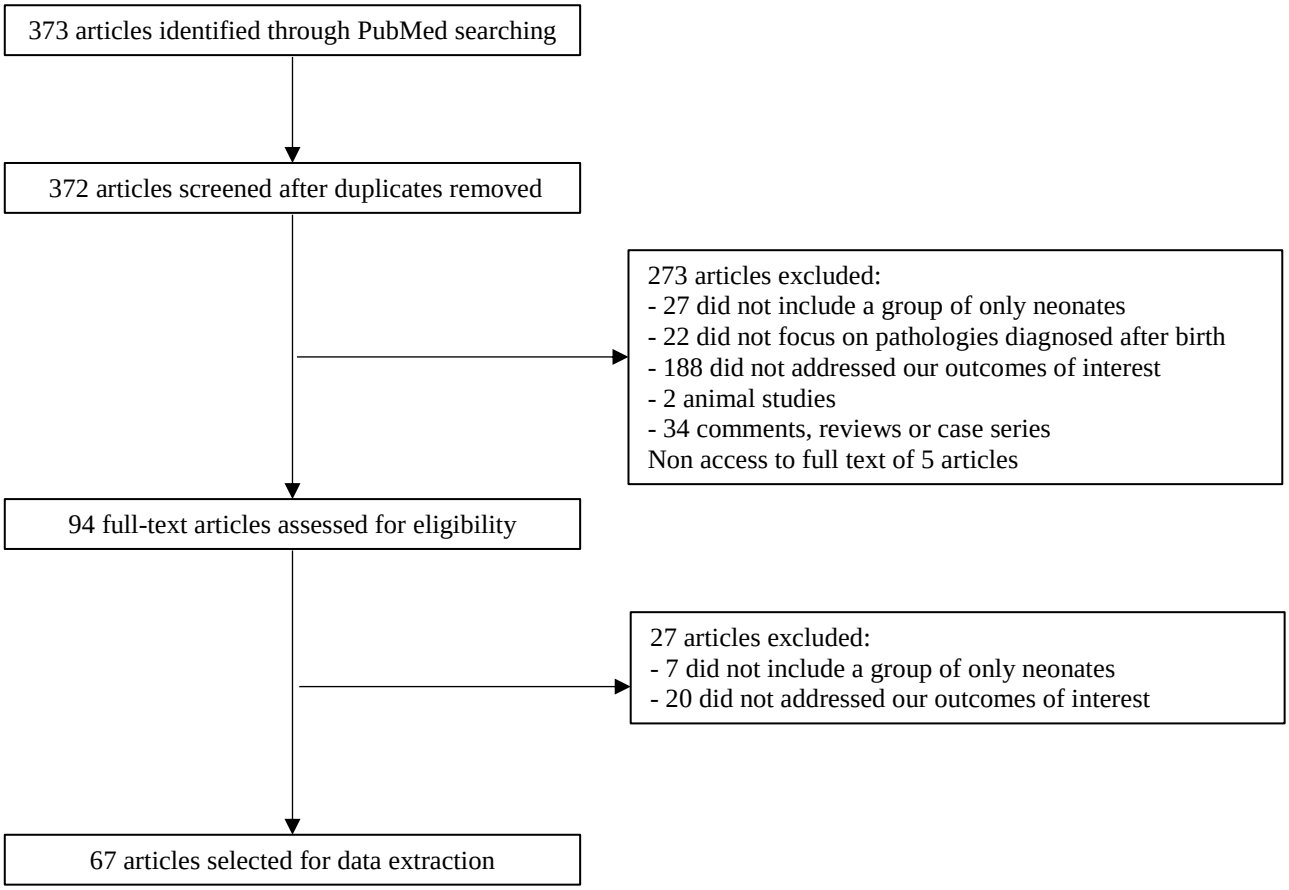
	BNP/NTproBNP	**Troponin I/T**	**CKMB**	Clinical Relevance
PDA	↑	↑		Diagnosis of PDA and hsPDA Individualized therapy and monitoring Complications and mortality
CHD	↑	↑		Indicator of myocardial compromise (contractility) [a] Inotropic support after birth [b]
PH	↑			Diagnosis Treatment (inhaled NO) Mortality
RD	↑	↑		Indicator of myocardial damage [a] Treatment (oxygen, ventilatory and inotropic support) [a] Severity [a] Mortality [a]
BPD	↑			Severity Mortality
PA		↑	↑	Indicator of myocardial damage Treatment (inotropic support) [a] Severity Mortality [a]
HIE		↑	↑	Severity [a] Mortality [a]

PDA: Patent Ductus Arteriosus; hsPDA: hemodynamically significant patent ductus arteriosus; CHD: congenital heart defect; PH: pulmonary hypertension; RD: respiratory distress; BPD: bronchopulmonary dysplasia; PA: perinatal asphyxia; HIE: hypoxic ischemic encephalopathy

[a] *Only for Troponin I/T*

[b] *Only for cord blood BNP*

Figure 1 *Flowchart of the systemic review*



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ANEXOS

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